Energetic Competition in the Complexation Affinity of Paracetamol with Other Molecules

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The intermolecular interactions of active pharmaceutical ingredients (APIs) are the driving forces of API molecular activity in solid crystal structure and stability, *in vivo* receptor binding, and in environmental transport and persistence. In API manufacturing, complexation of the API with another molecule (cocrystal conformer) to create stable crystalline structures that have the desired physical-chemical properties for manufacturing, storage, and further processing can be a useful tool, but the possibility of more energetically stable complexes forming instead of the target conformation can lead to undesired changes to the properties of the final product. Natural complexation of the API to cocrystal conformers in the environment can cause undesirable accumulation of the API. Using Density Functional Theory (DFT), the paracetamol and oxalic acid (PCA-OXA) cocrystal was studied to determine how hydrogen bonding dictates the formation of molecular complexes. Three different functionals were employed (B3LYP, M06-2X, and ωB97-XD) with and without correction for long range dispersion forces (D3). The hydrogen bonding sites of PCA-OXA were investigated to determine strength and overall contribution of H-bonding during nucleation by relaxing the geometries and evaluating structural and energetic changes. Complexation and configuration energies were calculated for 1:1 PCA-OXA, PCA-Water, and OXA-Water complexes. Results showed significant shortening of the hydrogen bonds within the PCA-OXA complex with large changes in energy during complexation of oxalic acid with paracetamol. Explicit solvation with water was used to investigate the energetic competition of oxalic acid and water at the H-bonding sites of paracetamol. Results show that the hydrogen donating sites of oxalic acid dominate the complexation of paracetamol. Among others, future work will concentrate on the analysis and comparisons of results obtained within an implicit solvation environment, energetic behavior of larger PCA-OXA oligomers, inspection of IR spectra, analysis of thermochemical data, the possible occurrences of transition states, the analysis of the HOMO-LUMO gap to determine chemical reactivity, and NMR spectral shifts.